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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID K. GONG, JAYNE E. HASTEDT,
ROBERT G. SCHAUB, NICHOLAS W. WARNE, ANDREW J. DORNER,
CHANDRA A. WEBB, and JAMES C. KEITH

Appeal 2009-001970
Application 10/820,656
Technology Center 1600

Decided: November 24, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 29, 32, 33, 36, 37, and 40. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claim 29 is representative of the claims on appeal, and reads as follows:

29. A method of preventing hemophilic bleeding in advance of a bleeding event, said method comprising:

a) aerosolizing a monomeric Factor IX (FIX), wherein the aerosolized monomeric FIX: i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm, ii) has a fine particle fraction percent less than 3.3 μm (FPF %<3.3 μm) of at least 50%, iii) is at least 90% monomeric, iv) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and v) is a dry powder having less than 10% water (wt/wt), but does not have ethanol;

b) slowly maximally inhaling aerosolized monomeric FIX; and

c) allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue to provide sufficient FIX to prevent bleeding for at least 100 hours after administration.

The Examiner relies on the following evidence:

Huang	US 6,280,729 B1	Aug. 28, 2001
Lechuga-Ballesteros (Lechuga)	WO 01/32144 A1	May 10, 2001

Kurachi et al., *Biology of factor IX*, 4 BLOOD COAGULATION AND FIBRINOLYSIS 953-974 (1993).

Appellants rely on the following evidence:

Gupta et al., Pulmonary Delivery of Human Protein C And Factor IX, Oxygen Transport to Tissue XVIII, Chapter 55, p. 429-35 (1997).

We affirm.

ISSUES

The Examiner concludes that the method of claim 29 is rendered obvious by the combination of Lechuga and Kurachi.

Appellants contend that the Lechuga, either alone or as combined with Kurachi, does not teach or suggest all of the limitations of the method of claim 29. Appellants contend further that even if the Examiner set forth a prima facie case of obviousness, the prima facie case has been rebutted by evidence of unexpected results.

Thus, the issues on appeal are:

1) Have Appellants demonstrated that the Examiner erred in concluding that Lechuga, either alone or as combined with Kurachi, teaches or suggests all of the limitations of the method of claim 29? and;

2) Have Appellants demonstrated that the Examiner erred in concluding that the evidence of unexpected results is not sufficient to rebut the prima facie case?

FINDINGS OF FACT

FF1 The Specification teaches that inhalation may provide a route of administration of coagulation factors, and would not require the use of needles (Spec. ¶10).

FF2 According the Specification, "[t]he most important parameter that defines the site of deposition of aerosol proteins within the respiratory tract is the particle characteristics of the aerosol," such as the mass median aerodynamic diameter (MMAD) (*id.* at ¶11).

FF3 The Specification notes that the use of nebulizers to administer biopharmaceuticals has important limitations (*id.* at ¶15). For example, the Specification notes, "the process of nebulization exerts high shear stress on the compounds, which can lead to protein denaturation." (*Id.*)

FF4 The present invention is thus drawn to:

> [A] method of treating hemophilia, with an aerosolized Factor IX (F.IX), wherein the aerosolized F.IX has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm, a fine particle fraction percent less than 3.3 μm (FPF%<3.3 μm) of at least 50%, is at least 80% monomeric protein, an after-aerosolization activity/pre-aerosolization activity of at least 80%; and is a dry powder having less than 20% water (wt/wt). The aerosol is slowly maximally inhaled to deposit the F.IX in the deep lung tissue, followed by maximal exhalation.

(*Id.* at ¶21.)

FF5 The Specification teaches that a preferred embodiment "uses a surface active di- or tripeptide as a excipient," wherein especially preferred is a di- or tri-leucyl excipient (*id.* at ¶24). In addition, the Specification teaches the use of a dry powder aerosolized formulation (*id.* at ¶59) produced by spray drying (*id.* at ¶62).

FF6 The Specification studied the *in vivo* activity of a formulation containing rFIX (recombinant factor IX)-45%; grFIX (glycosylated recombinant factor IX)-52.6%; NaCitrate 7.4%; and tri-leucine 40% (*id.* at ¶84) (the makeup of formulation 6 may be found at ¶61)).

FF7 Figure 8 of the Specification is reproduced below.

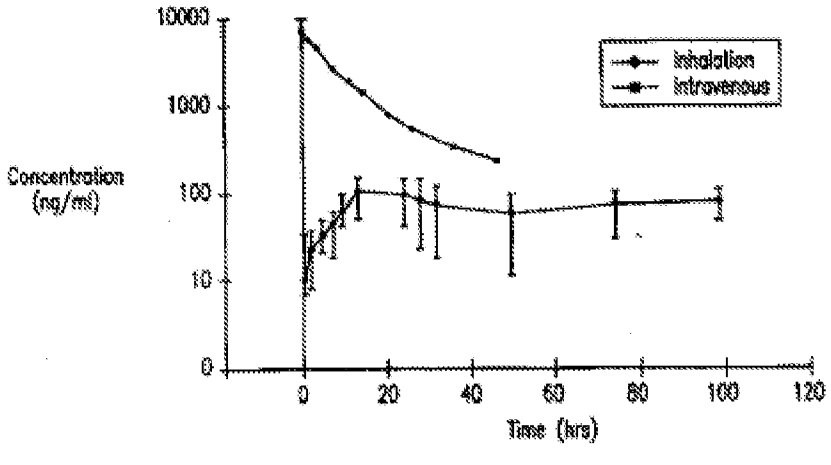

FIG. 8

Figure 8 shows "Mean Corrected rF.IX Antigen Concentration Time Curve for Tolerized Hemophilia B Dogs (n=3) Receiving rF.IX (50 IU/kg) by Inhalation." (*Id.* at ¶37.[1]) We can find no further discussion of this Figure in the Specification.

FF8 The Examiner rejects claims 29, 33, 37, and 40 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Lechuga-Ballesteros and Kurachi (Ans. 4). As Appellants do not argue the claims separately, we focus our analysis on claim 29, and claims 33, 37, and 40 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF9 The Examiner cites Lechuga for teaching "dry powder compositions having improved dispersivity comprising an active agent and a dipeptide or tripeptide comprising at least two leucyl residues." (Ans. 5.)

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[1] It appears as if Figure 8 as submitted by Appellants with the Appeal Brief is referred to as Figure 7 in the "Brief Description of the Drawings."

FF10 The Examiner finds that Lechuga specifically teaches a dry powder formulation comprising Factor IX, buffer, and trileucine (*id.* (citing Lechuga 44, Example 7)). The Examiner finds that Lechuga teaches that the dry powder formulations generally have a moisture content below 20%, and preferably below 6% (Ans. 6).

FF11 The Examiner notes that Lechuga teaches the use of aqueous solutions to prepare the dry powder, and that "'aqueous' does not imply or require the presence of alcohol (i.e. ethanol)." (*Id.* at 9.)

FF12 The Examiner finds that Lechuga teaches that the dry particles have a mass median diameter between 0.1 to 5 microns, and a mass median aerodynamic diameter (MMAD) less than 10 microns, and preferably between 1.5 to 3.5 microns (*id.* at 6; *see also* Lechuga at 3).

FF13 The Examiner further finds that Lechuga teaches that the dry powder formulations have an emitted dose (ED) greater than 40%, and often greater than 55%, and the use of the dipeptide or tripeptide comprising at least two leucyl residues "was effective, in all cases, to increase the ED value of the resultant compositions, and in some cases, doubling the ED value." (Ans. 6.)

FF14 The Examiner also finds that Lechuga's dry powder formulations are characterized by a particle dose or fraction (FPD or FPF) (the percentage of the powder having an aerodynamic particle less than 3.3 microns) ranging from 35% to 85%, and "are thus extremely effective in reaching the regions of the lung, including the alveoli." (*Id.* at 7; *see also* Lechuga at 7.)

FF15 The Examiner finds further that "slowly, maximally inhaling" is "conventional in the inhalation administration of pharmaceutical formulations." (Ans. 14.)

FF16 The invention of Lechuga is "based upon the discovery of a particular class of excipients, which, when incorporated into dry powder formulations for aerosolization and delivery to the lung, notably improves the dispersivity and aerosolization properties of the dry powders, irrespective of the type of active agent contained in the formulation." (Lechuga at 2.)

FF17 Lechuga teaches that the dry powder formulations are prepared by spray drying, wherein the aqueous formulations used in the process may optionally contain a water-miscible solvent, such as an alcohol (*id.* at 17).

FF18 Lechuga teaches that the compositions are useful "for treating or preventing any condition responsive to the administration of [the] active agent." (*Id.* at 24.)

FF19 Lechuga specifically teaches a dry powder formulation of Factor IX, "a 55,000 dalton glycoprotein with a modular domain structure . . . useful in the treatment of hemophila B." (*Id.* at 44.)

FF20 The formulations prepared by Lechuga are shown below.

Table 15. Factor IX Powders

Formulation	Emitted Dose (RSD)	MMAD
93% Factor IX/7% NaCitrate	57 (5 %)	-
37% Factor IX/3% Na Citrate/60% Leucine	78 (3%)	2.9
56% Factor IX/4% Na Citrate/40% Trileucine	89 (5%)	2.7

(*Id.*)

FF21 The Examiner also finds, citing Kurachi, that the biologically active form of Factor IX is monomeric (Ans. 7).

FF22 The Examiner notes:

> Lechuga does not explicitly teach or disclose anticipatory methods of treating hemophilia, preventing bleeding associated with a hemophilic assault as stated in the instant claims, specify the treatment of hemophilia B, teach monomeric percentage of FIX, the step of "slowly maximally inhaling", or the "step" of "allowing said monomeric FIX to deposit in the deep lung tissue."

(Ans. 8.)

FF23 The Examiner concludes that it would have been obvious to use the formulation of Lechuga to treat hemophilia using Factor IX as "Factor IX is a well-known active agent used in the treatment of Hemophilia B . . . and is one of the active agents that Lechuga teaches may be delivered using any suitable dry powder inhaler (DPI), an inhaler device utilizing the patient's inhaled breath as a vehicle to transport the dry powder drug to the lungs." (*Id.*)

FF24 The Examiner further concludes that it would have been obvious to use the composition of Lechuga to prevent hemophilic bleeding as that is the logical step after using the composition for treatment (*id.* at 9).

FF25 The Examiner also rejects claims 32 and 36 under 35 U.S.C. § 103(a) as being obvious over the combination of Lechuga and Kurachi as further combined with Huang (*id.*).

FF26 Gupta, published in 1997, teaches that inhalation "has proven capable of delivering even large macromolecules with acceptable bioavailabilities." (Gupta 429.)

FF27 Gupta teaches that Factor IX is a single chain glycoprotein, and teaches further that Hemophilia B patients are treated periodically with IV injections of Factor IX to control bleeding episodes (*id.* at 430).

FF28 Gupta teaches that a "less invasive dosage regimen would enable the prophylactic maintenance of homeostatic control, which would prevent joint degeneration and greatly enhance the quality of life for the hemophilia B patient." (*Id.*)

FF29 Gupta teaches that "[f]ormulation of proteins into MDI's [metered dose inhalers] and DPI's [dry powder inhalers] is a formidable task because dehydration and subsequent communition [sic, comminution] of proteins to produce powders in the size range suitable for inhalation *may* lead to loss of activity." (*Id.* (emphasis added).)

FF30 Gupta teaches that "[i]n order for the protein to be absorbed systemically, the administration technique must maximize drug deposition in the pulmonary region," and that a MMAD of less than 5 microns after slow inhalation allows deposit of 70% of the discharged dose into the respiratory tract (*id.* at 431).

FF31 Gupta tested a nebulizer apparatus for delivery of Factor IX, finding that Factor IX was not active, which the authors hypothesized was due to denaturation of the protein by shear forces imposed by the nebulizer or the large air water interface produced during nebulization (*id.* at 433).

FF32 Gupta added the excipient bovine serum albumin to increase the activity of the nebulized Factor IX (*id.* at 434).

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007), the Supreme Court rejected a rigid application of a teaching-suggestion-motivation test in the obviousness determination. The Court emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

In addition,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

Id. at 421.

Moreover:

> *Where . . . the claimed and prior art products are identical or substantially identical,* or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed

> product…. Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977) (emphasis added.)

The burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). It is well settled that results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). "[H]owever, when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (emphasis in original).

ANALYSIS

Appellants assert:

> [T]he following elements are . . . not found in the cited art:
> i) preventing hemophilic bleeding in advance of a bleeding event
> ii) at least 90% monomeric after-aerosolization
> iii) 80% activity retained after-aerosolization
> iv) does not have ethanol
> v) slowly maximally inhaling.

(App. Br. 11-12; *see also id.* at 15.)

Appellants argue that "these elements are merely assumed to exist in Lechuga or are allegedly obvious based on Lechuga, even though the formulation taught therein is not identical and even though Lechuga goes no further than making a dried powder, and neither tests its activity, nor uses it in any treatment." (*Id.* at 12.) Appellants assert that as the formulation described by Lechuga and the closest formulation taught by the instant Specification are not identical, as shown in the chart below prepared by Appellants:

Lechuga	Closest Formulation Described in 10/820,656
37% FIX, 3% NaCitrate, 60% Leucine	32.6% FIX, 7.4 % NaCitrate, 60% Leucine
56% FIX, 4% NaCitrate, 40% Trileucine	52.6% FIX, 7.4 % NaCitrate, 40% Trileucine

Appellants argue that "[o]ne cannot assume that the Lechuga FIX has the requisite properties because . . . the preparation method [is] unknown." (*Id.* at 14.)

Appellants assert that the Examiner relies on inherency to make up the claimed elements not taught or suggested by the prior art and, while noting that "[i]nherency can be used to supply a missing element that is not expressly taught in the art, but which nonetheless must be present and would be understood to be present in the prior art," assert that they "know of no case where inherency was used to provide at least seven of eleven claimed elements." (*Id.*) Thus, Appellants argue, "[t]here is simply no basis to assume that the powder of Lechuga has all of the recited characteristics and would be sequestered in the lung sufficient to provide for at least 100 hours

of dosing." (*Id.* at 16.)[2]

Appellants' arguments have been carefully considered, but are not found convincing. Claim 29 recites:

> A method of preventing hemophilic bleeding in advance of a bleeding event, said method comprising:
>
> a) aerosolizing a monomeric Factor IX (FIX), wherein the aerosolized monomeric FIX: i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm, ii) has a fine particle fraction percent less than 3.3 μm (FPF %<3.3 μm) of at least 50%, iii) is at least 90% monomeric, iv) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and v) is a dry powder having less than 10% water (wt/wt), but does not have ethanol;
>
> b) slowly maximally inhaling aerosolized monomeric FIX; and
>
> c) allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue to provide sufficient FIX to prevent bleeding for at least 100 hours after bleeding.

Lechuga teaches a Factor IX formulation for aerosolizing Factor IX, which has a MMAD between 1.5 to 3.5 microns, and specifically

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[2] Appellants further assert that the Examiner need declare under oath the alleged facts that the "formulations of Lechuga are 'substantially the same' and that 'Lechuga's FIX dry powders are deemed to have the same properties," and thus are assumed to have the claimed properties" (App. Br. 16). Appellants assert that the statements are mere argument and have been rebutted by competent evidence, such as Gupta (a prior art publication) (*id.* at 16-17). We conclude, however, that the preponderance of the evidence of record supports the Examiner's conclusion, *see*, *e.g.*, *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office), and thus the burden was properly shifted to Appellants to demonstrate the unobviousness of the method of claim 29.

exemplifies formulations having MMADs of 2.9 and 2.7 microns. In addition, Lechuga teaches that the formulations prepared according to the invention have a FPF less than 3.3 μm between 35% to 85%. Lechuga also teaches that the dry powder has a moisture content preferably below 6%, and that the dry powder is formed by spray drying an aqueous solution, which may or may not contain an alcohol, such as ethanol. Thus, Lechuga teaches the use of an aqueous solution that does not contain ethanol.

Lechuga does generically teach that the dry powder formulations of the invention may be used to treat or prevent any condition responsive to the administration of the active agent, but does not specifically teach prevention of hemophilia B. But the Examiner concludes that it would have been obvious to do so based on the teachings of Lechuga, and we agree. That conclusion is supported by Gupta, cited by Appellants, which teaches the prophylactic use of Factor IX to prevent joint degeneration and greatly enhance the quality of life for the hemophilia B patient.

As to the limitation that the Factor IX is 90% monomeric after-aerosolization and retains 80% activity after-aerosolization, we agree with the Examiner that the dry powder formulation of Lechuga is very similar to the formulations prepared by the instant Specification, using the same excipients (NaCitrate and trileucine), such that the ordinary artisan would expect the formulation of Lechuga to have the same properties as the claimed formulation, such as the Factor IX being present as a monomer and having 80% activity retained after-aerosolization. While Appellants argue that conclusion is in error as the method used by Lechuga to prepare the formulations is unknown, Lechuga specifically teaches spray drying an

aqueous solution without the use of ethanol to prepare the dry powder formulations, wherein the formulation obtained by Lechuga has the MMAD, FPF, and water content as required by claim 29.

As to the limitation of slowly, maximally inhaling, we agree with the Examiner that "slowly, maximally inhaling" is conventional in the inhalation administration of pharmaceutical formulations. That finding is also supported by Gupta, which teaches that for the protein to be absorbed systemically, the administration technique must maximize the deposition in the pulmonary region, and that a MMAD of less than 5 microns after slow inhalation allows deposit of 70% of the discharged dose into the respiratory tract.

Appellants argue further that the prior art does not teach or suggest the elements of "'allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue' and 'providing sufficient FIX to prevent bleeding for at least 100 hours after administration.'" (App. Br. 11.) Appellants assert that "[a]ssuming both sequestration and 100 hour dosing is a clear application of hindsight reasoning." (*Id.* at 19.)

First, as to the limitation of "allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue," as noted by the instant Specification, "[t]he most important parameter that defines the site of deposition of aerosol proteins within the respiratory tract is the particle characteristics of the aerosol," such as the mass median aerodynamic diameter (MMAD) (FF2), and Lechuga teaches a Factor IX formulation that has the same particle characteristics of

the aerosol, such as the MMAD, as required by the claim. Moreover, as evidenced by Gupta, it was also known that a MMAD of less than 5 microns after slow inhalation allows deposit of 70% of the discharged dose into the respiratory tract. Thus, as Lechuga teaches a formulation as required by claim 29, and the method of administration is known in the art, the result of administering that formulation would be the same, that is, "allowing said monomeric FIX to deposit in the deep lung tissue such that said monomeric FIX is sequestered in said deep lung tissue."

As to the limitation that the process provides "sufficient FIX to prevent bleeding for at least 100 hours after administration," that is a result of the process suggested to the ordinary artisan by Lechuga, and not a positive recitation of a dosing regimen, and thus does not limit the claimed method. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

Appellants argue further that the Examiner's reliance on Kurachi is irrelevant, as Kurachi teaches that FIX is a monomer *in vivo*, but does not address "what the dried, aerosolized FIX will look like." (App. Br. 12.) Appellants rely on Gupta for its teaching that formulation of proteins into dry powder inhalers is a formidable task because "'dehydration and subsequent communition [sic] of proteins to produce powders in the size range suitable for inhalation may lead to loss of activity.'" (*Id.* at n. 12 (quoting Gupta).) Appellants assert further that Lechuga does not test the formulation relied upon by the Examiner for activity, and as other

publications teach that drying of proteins such as FIX cause clumping, there is no reasonable expectation of success of arriving at the method of claim 29 (App. Br. 17).

Appellants assert further that Gupta teaches away from the claimed invention, as Gupta is the "only prior art effort to aerosolize FIX and determine its subsequent activity," teaching that "FIX was denatured when aerosolized." (*Id.* at 20.) In response to the Examiner's finding that "'the problems associated with the nebulization of aqueous solutions of proteins (e.g. Factor IX) are irrelevant with regards to the suggested methods of Lechuga,'" Appellants assert that "the formulation made by the inventors is also liquid prior to being dried, and the potential for loss of activity is similarly present." (*Id.*)

As discussed above, Lechuga teaches a dry powder formulation that is very similar to the dry powdered formulations prepared by the instant Specification, using the same excipients (NaCitrate and trileucine), such that the ordinary artisan would expect the formulation of Lechuga to have the same properties as the claimed formulation, such as the Factor IX being present as a monomer. Moreover, Lechuga recognizes that the active form is monomeric, thus Lechuga expected the Factor IX to be present in the formulation as monomer.

Gupta does not persuade us otherwise. Gupta teaches that "[f]ormulation of proteins into MDI's [metered dose inhalers] and DPI's [dry powder inhalers] is a formidable task because dehydration and subsequent communition [sic] of proteins to produce powders in the size range suitable for inhalation *may* lead to loss of activity" (FF29), and not

that the formulation always leads to loss of activity. In Gupta, most of the loss of activity is caused by the nebulization process (FF31), which is not relevant to the use of a dry powder inhaler. Thus, in the instant case, Lechuga teaches a spray dried formulation of Factor IX that is very similar to the formulations prepared by the instant Specification, meeting the requirement for the formulation as required by claim 29 (see discussion above). In addition, Lechuga specifically teaches that the formulations are to be used for treating or preventing any condition responsive to the administration of the active agent, in this case Factor IX. Thus, the rejection set forth by the Examiner clearly suggests the use of the Factor IX formulation as taught by Lechuga for the prevention of hemophilic bleeding in advance of a bleeding event, as required by claim 29.

At worst, it would have been obvious to try and administer the formulation of Lechuga for the prevention of hemophilic bleeding in advance of a bleeding event. Lechuga suggests a formulation that meets the limitations of the formulation required by claim 29, and suggests its use of a treatment or a prophylactic; thus Lechuga teaches an identified solution, and the ordinary artisan would have a good reason to pursue that known solution to solve the art recognized problem of preventing hemophilic bleeding in advance of a bleeding event. *See Bayer Schering Pharma AG v. Barr Labs, Inc.*, 575 F.3d 1341, 1347-50 (Fed. Cir. 2009) (following *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988) in finding that the claimed invention was "obvious to try" within the meaning of *KSR*).

Appellants also assert that the present methods demonstrate unexpected results (App. Br. 21). According to Appellants, the

"pharmacokinetic profile of inhaled FIX is a significant (and surprising) improvement over the intravenous FIX profile because it avoids the large initial dose and thus clotting difficulties due to the initial high dose of FIX . . ., and because the dose remains constant for at least 100 hours." (*Id.*) Appellants rely on Figure 8 of the Specification to support their assertion of unexpected results, arguing further that "based on the surprisingly flat pharmokinetics shown in Figure 8, one would expect that the FIX would remain sufficiently high to prevent excess bleeding for at least one week." (*Id.*)

Appellants argue further that the Examiner erred in dismissing the results as they pertain to injection of FIX and not inhalation, asserting that "the BeneFix package inserts showing an 18-20 hr half life is the closest prior art relating to the treatment element" as the Examiner has not cited prior art demonstrating treatment (*id.* at 22).

Appellants' assertion of unexpected results has been considered, but there is no evidence that we can find, either in the Specification or presented as a declaration, that the formulation used to produce the results shown in Figure 8 meets the limitations of claim 29, or that the ordinary artisan would consider such results unexpected. Thus, Appellants have not met the burden of demonstrating unexpected results for the claimed method.

As to the rejection of claims 32 and 36 under 35 U.S.C. § 103(a) as being obvious over the combination of Lechuga and Kurachi as further combined with Huang, as Appellants do not separately argue that rejection, we affirm that rejection.

CONCLUSION(S) OF LAW

We conclude that

1) Appellants have not demonstrated that the Examiner erred in concluding that Lechuga, either alone or as combined with Kurachi, teaches or suggests all of the limitations of the method of claim 29; and

2) Appellants have not demonstrated that the Examiner erred in concluding that the evidence of unexpected results is not sufficient to rebut the prima facie case.

We thus affirm the rejection of claim 29, under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Lechuga-Ballesteros and Kurachi. As claims 33, 37, and 40 stand or fall with claim 29, we affirm the rejection as to those claims as well.

As to the rejection of claims 32 and 36 under 35 U.S.C. § 103(a) as being obvious over the combination of Lechuga and Kurachi as further combined with Huang, as Appellants do not separately argue that rejection, that rejection is also affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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